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Differences in pituitary-adrenal reactivity in Black and White men with and without alcohol use disorder

Julianne L. Price[a,b,*], Ian R. Frazier[a], Ben Lewis[b], Robrina Walker[c], Martin A. Javors[d], Sara Jo Nixon[a,b], Bryon Adinoff[c,e]

[a] University of Florida, Department of Psychology, United States
[b] University of Florida, Department of Psychiatry, United States
[c] University of Texas Southwestern Medical Center, Department of Psychiatry, United States
[d] University of Texas Health Science Center, Departments of Psychiatry and Pharmacology, United States
[e] VA North Texas Health Care Systems, United States

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ABSTRACT

Background: Treatment-seeking men with alcohol use disorder (AUD) classically exhibit a blunted hypothalamic-pituitary-adrenal (HPA) axis response to pharmacologic and behavioral provocations during the early phases of abstinence from alcohol. Independent of alcohol, a significant muting of HPA axis reactivity is also observed among racial minority (e.g. Black) individuals. The effect of AUD upon the altered HPA axis response of racial minority individuals has not been explored. The current work represents a secondary analysis of race and AUD status among a sample of men.

Methods: Healthy male controls (17 White, 7 Black) and four-to six-week abstinent men with AUD (49 White, 13 Black) were administered a psychosocial stressor and two pharmacologic probes [ovine corticotropin releasing hormone (oCRH) and cosyntropin] to assess HPA axis reactivity. Plasma cortisol and adrenocorticotropin hormone (ACTH) were assessed at 10–20 min intervals prior to and following behavioral and pharmacological stimulation. Basal and net-integrated responses following provocations were analyzed to identify potential group differences. A measure of childhood adversity was also obtained to consider the implications of prior stressors upon HPA axis function.

Results: A three-fold increase in oCRH-induced ACTH was seen in Black men relative to White men regardless of AUD status. Adversity exerted a dampening effect on this pituitary sensitivity within Black controls only. Adjusted for adversity, a significant blunting effect of AUD status on ACTH reactivity was identified within White participants following oCRH. No group differences were present following cosyntropin administration. In response to the psychosocial stressor, White, but not Black, men with AUD experienced the expected blunting of cortisol reactivity relative to White controls. Rather, Black men with AUD exhibited greater cortisol reactivity relative to White men with AUD.

Conclusions: Differences in HPA axis reactivity associated with race were present in men with and without AUD. Explanatory biological mechanisms of the relationship between alcohol use and/or stress, in both healthy and unhealthy populations, may require a reassessment in different racial populations.

1. Introduction

Individuals with alcohol use disorder (AUD) display a wide array of neurophysiological disturbances, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. However, other contributing factors have been shown to influence this dysregulation including sex (Adinoff et al., 2010; Kudielka and Kirschbaum, 2005) and psychopathology (Brady et al., 2006). Racial minority status, although implicated in altered HPA axis function (Chong et al., 2008; Skinner et al., 2011), has never been evaluated as a potential factor in AUD-related HPA axis dysregulation.

The physiologic response to stress is regulated by the glucocorticoid cascade of the HPA axis. Central activation of the hypothalamic corticotropin-releasing-hormone (CRH) triggers adrenocorticotropin hormone (ACTH) release from the anterior pituitary. ACTH in turn stimulates cortisol secretion from the adrenal cortex, which then acts as

* Corresponding author at: University of Florida, Department of Psychiatry, PO Box 100256, Gainesville, FL, 32610, United States.
E-mail address: JulianneLP@ufl.edu (J.L. Price).

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an inhibitory feedback signal, deactivating the system at both the hypothalamic and pituitary levels. Repeated activation of the HPA axis from exposure to chronic stressors can lead to long-lasting alterations of the system, commonly identified by blunted ACTH and cortisol reactivity to stress (Herman et al., 2003; McEwen, 1998; Stephens and Wand, 2012).

During acute and chronic alcohol intoxication and withdrawal, heightened HPA axis reactivity in response to pharmacologic stimulation and acute-stress is observed in men with AUD (Adinoff et al., 2003; Heinz et al., 1995). Following approximately one week of abstinence from alcohol, blunted ACTH and cortisol reactivity are present and continue through protracted abstinence (Adinoff et al., 2005a; Blaine and Sinha, 2017; Lovallo et al., 2000). These noted alterations to the stress response system have been shown to predict increased craving, decreased length of abstinence, and greater relapse severity (Adinoff et al., 2017; Breese et al., 2005; Junghanns et al., 2003). However, only a handful of studies reported a non-White sample. The maximum racial minority participation rate was < 30% (Adinoff et al., 2003: 20% Black participants;Brady et al., 2006: 13% Black participants;Sinha et al., 2011: 25% Black participants; Sinha et al., 2011: 18% Non-White participants) and none of these studies examined the potential influence of race on HPA axis functioning.

Independent of alcohol use, the literature on racial differences in HPA axis function has notably expanded in the last decade. Relative to healthy White controls, healthy Black controls display flatter diurnal cortisol slopes (Hajat et al., 2010; Skinner et al., 2011) and decreased ACTH and cortisol provocation following a psychosocial stressor (Chong et al., 2008). The racial differences in HPA axis function are highly associated with measures of stress and emerge around late adolescence (Skinner et al., 2011; Krieger, 2005). For this reason, minority stress, rather than genetic differences, has been proposed as the underlying cause of the alterations in HPA axis reactivity seen in racial minorities. The chronic effects of minority stressors on mental and physical health outcomes have been characterized in Black Americans, carry significant public health implications (Clark et al., 1999; Jackson et al., 2016), and play an apparent role in the development of AUD (Keyes et al., 2011).

This post-hoc analysis stemmed from a study originally designed to assess the interaction between HPA axis reactivity, chronic stress, and drinking in treatment-seeking men and controls (Adinoff et al., 2017; Meng et al., 2011). Due to the inclusion of a considerable number of minority participants, we took this opportunity to explore race as a possible contributing factor in the dysregulation associated with AUD.

ACTH and cortisol were assessed in Black and White men with and without AUD following a psychosocial stress task (to assess an ecologically valid stimulation of the HPA axis) and the administration of oCRH (to assess a more specified activation at the pituitary level) and cosyntropin (to assess activation at the adrenal level). For this study, we examined basal levels and reactivity of endocrine response (i.e. ACTH and cortisol) for pharmacologic and acute-stress HPA activations. Due to previous work suggesting women with AUD do not display blunted HPA axis reactivity to provocation (Adinoff et al., 2010), their inclusion was not supported in the current work's parent study on HPA alterations and post-treatment drinking. For this reason, the current analyses are limited to men.

We anticipated a main effect of race to identify blunted HPA axis reactivity in Black men relative to White men. We further expected a main effect of AUD to show blunting in treatment-seeking men relative to controls. Of primary interest, we expected an interaction between race and AUD status in which Black men with AUD would show a multiplicative effect, exhibiting the greatest magnitude of hypoactivation of HPA axis reactivity. Moreover, factors associated with lifetime stress and adversity are related to HPA axis activity independent of race (Hajat et al., 2010; Lovallo et al., 2012) but may also speak to the differential impact of stressors on Black and White individuals' allostatic mechanisms (Krieger, 2005; Williams and Mohammed, 2009). We therefore included an exploratory analysis investigating the explanatory power of a measure of childhood adversity on the hypothesized relationship between race, AUD, and HPA axis reactivity.The assessment of childhood adversity provides a measure of external stressors that preceded the development of race-based differences in HPA axis function as well as the development of AUD in the clinical sample.

2. Methods and materials

2.1. General criteria

Selection criteria and methods have been reported previously (Adinoff et al., 2017). Participants were men between the ages of 21 and 59. Exclusionary criteria included a current diagnosis of a DSM-IV Axis I disorder [with the exception of substance use disorders for AUD participants and post-traumatic stress disorder (PTSD) for either group], use of medications known to affect the HPA axis or central nervous system (e.g. psychotropics, calcium channel blockers, hypoglycemics), and any medical condition that might affect HPA axis function (e.g. diabetes).

2.2. Participants with AUD

Sixty-two (49 White, 13 Black) non-Hispanic male participants with AUD were recruited from inpatient residential treatment programs at the VA North Texas Health Care System and Homeward Bound, Inc. (a public sector treatment program). Recruiting participants from the residential units allowed for monitoring of abstinence as participants remained on the unit prior to participation. AUD participants must have endorsed alcohol as their drug of choice, self-reported daily alcohol use of > 80 gm a day (e.g., six-pack of beer or half of a pint of 100-proof liquor) for at least two weeks prior to admission. Criteria for alcohol dependence was met per the Diagnostic and Statistical Manual on Mental Disorders [DSM-IV (First et al., 2002)].

2.3. Healthy control participants

Twenty-four healthy non-Hispanic male controls (17 White, 7 Black) without a lifetime history of Axis I substance dependence (with the exception of nicotine) or current Axis I non-substance dependence were recruited from the community.

2.4. Clinical assessment

The study was approved by the Institutional Review Boards at both the University of Texas Southwestern Medical Center and the VA North Texas Health Care System. Informed consent was obtained from all participants. All participants were assessed for Axis I disorders using the Structured Clinical Interview for DSM–IV Axis I Disorders—Lifetime Version [SCID (First et al., 2002)]. Participants with current Axis I Disorders were not included. Comorbid substance use disorders are listed in Table 1. Additional assessments included the Beck Depression Inventory [BDI (Beck et al., 1979)], State Trait Anxiety Inventory [STAI-S (Speilberger, 1971)] and Drinking Inventory of Consequences [DrInC (Miller et al., 1995)]. The Time Line Follow Back [TLFB (Sobell and Sobell, 1992)] estimated the number of drinking days and number of standardized drinks over the participants' lifetime and the daily drinking over the 90 days prior to recent abstinence. Participants were compensated for their participation.

2.5. Childhood adversity inventory

Participants completed the Childhood Adversity Inventory [CAI (Dienes et al., 2006)], a semi-structured interview focusing on seven areas of adversity occurring before the age of 13: separation or loss of

Table 1
Demographic and Clinical Characteristics (mean ± standard deviation or %).

	Controls		Alcohol Use Disorder	
	White n = 17	Black n = 7	White n = 49	Black n = 13
Age	44.2 ± 9.7	40.3 ± 7.9	42.3 ± 9.2	45.7 ± 6.8
Education[a]	15.4 ± 1.5	15.7 ± 1.3	12.3 ± 2.0	12.6 ± 1.2
% Nicotine Users[a]	5.9	14.3	81.6	76.9
% Full time Employed[a]	88	57	43	46
Marital Status				
% Single	29	71	43	31
% Married	35	29	6	8
% Divorced/Separated	24	0	51	46
% Other	12	0	0	15
Degree[a]				
% HS/GED	17	29	76	62
% Associates	24	14	14	38
% Bachelors	59	43	8	0
% Graduate	0	14	2	0
Childhood Adversity Index	9.7 ± 3.0	10.4 ± 4.3	11.4 ± 3.3	11.7 ± 4.5
BDI[a]	2.6 ± 2,8	.42 ± .79	9.5 ± 7.3	11.2 ± 7.8
STAI[a]	27.4 ± 7.5	25.0 ± 3.6	35.0 ± 6.4	33.1 ± 5.2
Current substance use disorders	0	0	8	5
Cannabis			6	0
Cocaine			4	4
Amphetamine			1	0
Opioid			0	1
Past 90 Days Drinking				
Total Drinks	15.5 ± 16.1	14.5 ± 13.5	1496.1 ± 955.0	1166.9 ± 1024.1
Drinking Days	7.5 ± 9.5	6.2 ± 4.9	78.6 ± 16.9	76.2 ± 15.9
Drinks/Drinking Day	2.8 ± 2.0	2.2 ± 0.9	18.8 ± 10.6	14.9 ± 13.3
Lifetime Drinking				
Total Drinks	6,541.7 ± 6,283.2	1,466.5 ± 1,732.4	110,428.3 ± 84,835.3	83,763.5 ± 47,758.1
Drinking Days	1,788.3 ± 1,674.537.7	625.7 ± 684.6	6,951.7 ± 3,320.8	8,010.0 ± 3,089.2
Drinks/Drinking Day	3.5 ± 2.0	2.8 ± 1.8	15.3 ± 7.2	11.0 ± 7.1
DrInC	9.8 ± 7.7	4.9 ± 0.9	39.3 ± 5.2	35. 5 ± 5.8

[a] Main effect of AUD status, $p < .05$.

the primary caretaker(s); significant loss of others and/or life-threatening illness or injury to others or self; physical neglect; emotional abuse or assault; physical abuse or assault; witnessing violence; and sexual abuse or assault. The interviewer follows structured prompts regarding each area of adversity gathering concrete behavioral aspects of each event and the level of impact the event had on the participant's life. Each domain is interviewer scored on a Likert scale of 1-5- one being no evidence of adversity, five being extreme adversity (Fink et al., 1995; Rao et al., 2008). Subscores are summed for an overall score of adversity ranging from 7 (no adversity present) to 35 (extreme adversity in all seven areas).

2.6. Assessment of HPA axis functioning

The Trier Social Stress Test [TSST (Kirschbaum et al., 1993)], cosyntropin infusion, and oCRH infusion were performed in separate sessions on sequential days (see Fig. 1). These provocations occurred at approximately 4–6 weeks of abstinence for participants with AUD. Procedures were conducted in the evening, allowing basal and provoked measures to be assessed during the diurnal period of stable quiescent in the absence of ACTH and cortisol morning escalations. Participants were provided transportation to the Clinical and Translational Research Center (CTRC) at the University at Texas Southwestern Medical Center (UTSW), where study procedures were performed. Nicotine-dependent participants were provided a nicotine patch upon arrival as smoking was not allowed throughout the study. An intravenous (IV) line was placed one hour prior to each study for plasma collection. The Brief Symptom Inventory [BSI (Derogatis and Melisaratos, 1983)] was obtained just prior to each procedure to assess psychological state prior to assessments.

2.6.1. oCRH stimulation

Basal measures of ACTH and cortisol were obtained every 10 min from 1930 to 2000 h. Intravenous (IV) oCRH 0.4 μg/kg was administered at 2001 h. over one minute; blood samples were then collected every 10 min for one hour and every 20 min for an additional hour. Four participants either did not complete the oCRH administration or were missing too many data points to calculate net-integrated response (1 White control, 2 White AUD, 1 Black AUD).

2.6.2. Cosyntropin stimulation

Basal measures of cortisol were obtained every 10 min from 1930 to 2000 h. An intravenous (IV) infusion of cosyntropin (0.1 μg/kg) was administered over one minute at 2001 h. Blood samples were collected every 10 min from 2000 to 2100 h followed by an additional hour of collection every 20 min. The cosyntropin model is limited to cortisol analyses as cosyntropin serves as an exogenous ACTH agent. Seven participants did not complete the cosyntropin infusion (1 White control, 1 Black control, 4 White AUD, 1 Black AUD).

2.6.3. TSST

Basal ACTH and cortisol plasma concentrations were obtained at 1845 and 1855 h. The procedure began at 1900 h and was performed as described by Kirschbaum et al. (1993). Post-task measures were obtained at 1920, 1930, 1940, 1950, 2000, and 2010 h. Six participants either did not complete the TSST or were missing too many data points to calculate net-integrated response (2 Black control, 3 White AUD, 1 Black AUD).

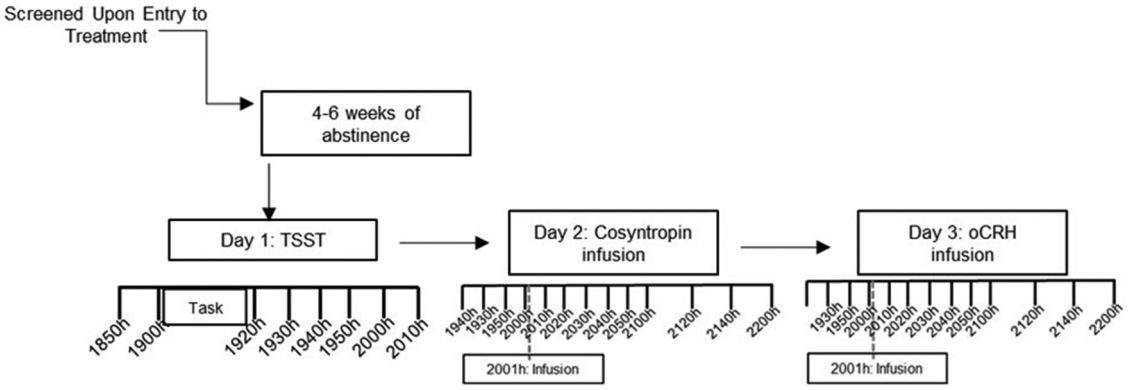

Fig. 1. Timeline of Screening and HPA Activation Procedures. Men with AUD were screened upon entry to a residential facility. Participants were monitored throughout the length of stay at the program. Between 4–6 weeks of abstinence, participants were transferred to the Clinical Research Unit at the University of Texas Southwestern Medical Center. On the evening of the first day, a catheter was inserted into the forearm to allow for multiple blood draws followed by a relaxation period. Participants then completed the Trier Social Stress Task (TSST). Participants were administered an IV dose of cosyntropin on the second day, and an IV dose of ovine cortiocotropin releasing hormone (oCRH) on the third day.

2.6.4. BioAssay

All ACTH and cortisol samples were tested in duplicate at the Biological Psychiatry Analytical Labs at the University of Texas Health Science Center (MAJ). For %CV values greater than 20%, a second set of duplicate samples were tested and the median of the four results was reported. Plasma (EDTA) ACTH was measured using an ELISA kit (Biomerica, Newport, CA). Calibrators included a 0 pg/mL sample, spiked calibrators ranged from 5 to 165 pg/mL, the lowest detectable concentration was 0.46 pg/mL. Intra-assay variability was 3.1%CV at 35.7 pg/mL (N = 21) and inter-assay variability was 5.8%CV at 35.2 pg/mL (N = 21). Plasma (EDTA) cortisol was quantified using an ELISA kit (Diagnostic Systems Labs, Webster, TX). Calibrators included a 0 µg/dL sample and spiked calibrators ranged from 0.5 to 60 µg/dL. The minimum detectable concentration was 0.1 µg/dL. Intra-assay variability was 5.0%CV at 15.9 µg/dL (N = 12) and inter-assay variability was 6.1%CV at 11.4 µg/dL (N = 12).

2.7. Statistical analyses

Statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC). All a priori alpha levels were established at .05. Demographic, alcohol use, and adversity variables were analyzed with 2 (group) × 2 (race) ANOVAs to test for pre-existing differences between race or AUD groups.

Missing neuroendocrine values were estimated based on the mean of hormone measures taken directly before and after the missing values. Basal measures were an average of the baseline collections (i.e. two time points for TSST, four time points for oCRH and cosyntropin). Neuroendocrine reactivity was expressed using the net-integrated response from baseline: area beneath the concentration-time curve from 0 to 60 min for TSST and 0 to 120 min for oCRH. Outliers within group as determined by three standard deviations were removed case wise from the analyses resulting in the removal of data points from three White AUD and one Black AUD participant from the TSST data and two AUD participants from the cosyntropin data (1 Black, 1 White).

For this secondary analysis, multivariate models evaluated the main and interactive effects of group and race on basal and provoked ACTH and cortisol secretion from each paradigm. Adversity (per the CAI) was then added to the models to assess improvement of fit (decrease in Akaike Information Criterion) and possible three-way interactions. Assumptions of regression were verified (.e.g. homoscedacticity, normality, multicollinearity). Due to the unequal sample sizes, all analyses were subjected to nonparametric transformation and re-analyzed. Pairwise comparisons remained significant, thus, for the purpose of clarity, statistics from the original models are reported within.

Wilk's Lambda, F-statistics, and p-values are reported for the omnibus tests. F-statistics and p-values are reported for significant univariate tests. For pairwise comparisons, t-statistics, p-values, Cohen's d effect sizes, and 95% confidence intervals are reported. Because pairwise analyses were limited to planned comparisons (i.e. White vs. Black controls; White vs. Black AUD; White controls vs. AUD; Black controls vs. AUD), t-tests are not corrected for multiple comparisons. In decomposing three-way interactions with adversity, beta weights are reported for each group. Improvement in fit statistics are reported as a chi-square comparison with the previous model and p-values.

3. Results

3.1. Demographics and drinking (Table 1)

The mean age for all participants was 43.0 ± 8.9 years old. There were no racial differences on age, body mass index, or socioeconomic factors including education, employment status, or marital status. Participants with AUD were more likely to be current smokers ($\chi^2_1 = 39.53$, $p < .0001$) less educated ($F_{1,92} = 140.55$, $p < .0001$), divorced ($\chi^2_5 = 209.86$, $p < .0001$), and less likely to be employed ($\chi^2_5 = 22.04$, $p = .0005$) relative to controls. As smoking severity (i.e. cigarettes/day) violated homogeneity of regression assumptions and socioeconomic factors (i.e. education, marital status, employment status) did not improve model fit (all $\chi^2_1 = 0$, $p = 1.0$), variables were not appropriate to serve as covariates (Yzerbyt et al., 2004) and were therefore not included in the analyses. Four participants had current diagnosable PTSD including two Black and two White men with AUD. These participants were not noted as outliers, nor did removal of the four participants detract from the significant findings; therefore, participants with PTSD were not excluded from the analyses.

As expected, participants with AUD consumed more alcohol over the prior six months relative to controls [drinks per drinking day ($F_{1,86} = 31.05$, $p < .0001$). There were no differences between racial groups on drinking measures and AUD severity.

3.2. Pituitary provocation (oCRH)

ACTH and cortisol response curves to oCRH are depicted in Fig. 2A and B, respectively. The omnibus multivariate models showed no main effect of AUD status for oCRH-induced ACTH but did identify a significant main effect of race (Wilk's $\lambda = .69$, $F_{2,77} = 16.99$, $p < .0001$). Despite there being no group differences on basal ACTH, the effect of race on oCRH-induced ACTH ($F_{1,78} = 32.09$, $p < .0001$) indicated that Black participants had nearly three-fold greater oCRH-induced ACTH

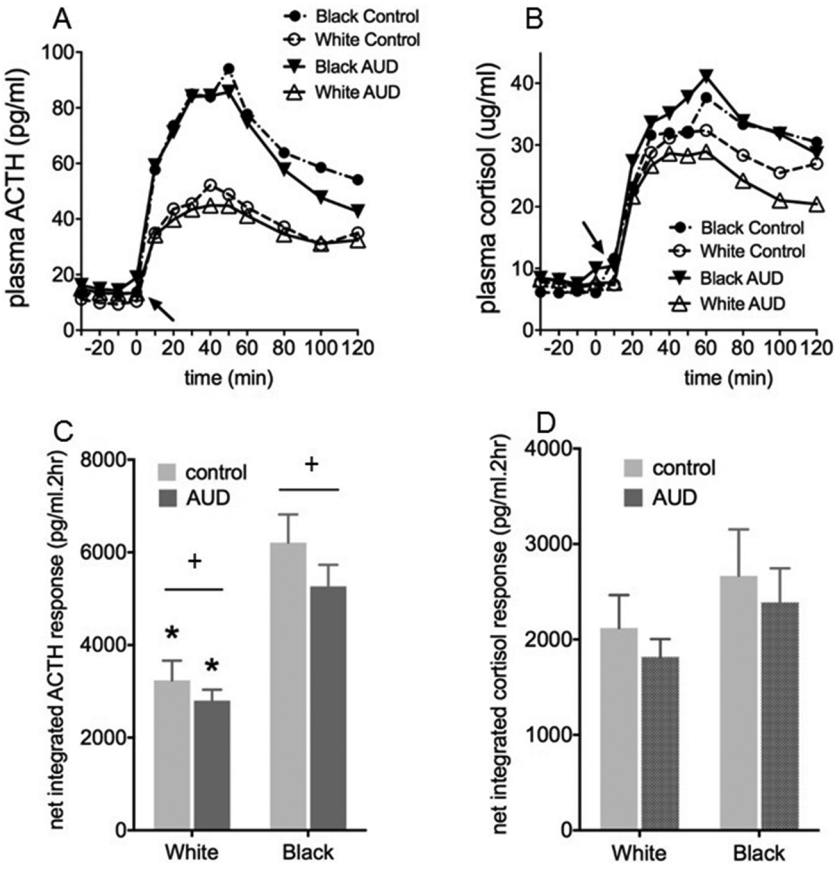

Fig. 2. ACTH and cortisol response to oCRH infusion. Top panel: Response curves for ACTH (A) and cortisol (B). Arrows indicate the time that the bolus was administered. No group differences were present in basal ACTH or cortisol. Black participants displayed a 3-fold greater oCRH-induced ACTH increase than White participants (p = .0002, d = 1.26). No group differences were present for oCRH-induced cortisol reactivity. Bottom Panel: Adversity adjusted means for net-integrated ACTH (C) and cortisol (D) response following oCRH infusion. + Black men exhibit greater pituitary sensitivity than White men following oCRH provocation, p = .004. *White men with AUD exhibit blunted oCRH-induced ACTH relative to White controls when controlling for adversity, p = .002. Error bars indicate standard error. There were no significant group differences on oCRH-induced cortisol.

reactivity than White participants (Fig. 2C. $t_{81} = 3.89$, p = .0002, d = 1.26; CI: 1796.49–3743.40).

Introducing adversity into the oCRH-ACTH model explained a significant proportion of the variance ($X^2_4 = 64.8$, p < .0001). The significant effect of race remained ($F_{1,74} = 13.51$, p = .0004) and a race X AUD status interaction (Fig. 2C. $F_{1,74} = 5.57$, p = .02) as well as a three-way interaction between race, AUD status, and adversity ($F_{1,74} = 4.83$, p = .03) emerged. The race X AUD status interaction indicated that when level of childhood adversity was controlled for, White men with AUD displayed a blunted oCRH-induced ACTH response relative to White controls (Fig. 2C: $t_{62} = 3.20$, p = .002, d = .45, CI: 354.20–1509.74). In decomposing the three-way interaction, there was no relationship between adversity and oCRH-induced ACTH within the White participants. However, within Black participants, adversity significantly interacted with AUD status (Fig. 3 $F_{1,18} = 7.32$, p = .02). This relationship was driven by the healthy Black controls, for whom there was a negative relationship between childhood adversity and oCRH-induced ACTH, explaining 55% of the variance (p = .05, $r^2 = .55$, $ß_{standardized} = -.74$). That is, healthy Black controls who experienced greater levels of childhood adversity displayed lower ACTH responsivity. The relationship between adversity and ACTH reactivity in Black men with AUD, though not significant, was inverse to that of the controls (p = .29, $r^2 = .12$, $ß_{standardized} = .35$).

The omnibus multivariate for oCRH-induced cortisol found no main or interactive effects of AUD status or race. Including adversity into the oCRH-induced cortisol model explained a significant portion of the variance ($X^2_4 = 48.0$, p < .001) and demonstrated a negative relationship between adversity and net-integrated cortisol that approached significance ($F_{1,75} = 3.12$, p = .08) suggesting that individuals with greater experiences of adversity had decreased cortisol reactivity. However, this effect did not differ by race or AUD status.

3.3. Adrenal provocation (cosyntropin)

The cortisol response curve to cosyntropin can be seen in Fig. 4A. The omnibus test indicated no main or interactive effects of race or AUD status for basal or cosyntropin-induced cortisol. Including adversity improved the model fit ($X^{2=}_4$ 45.2, p < .001), however there were no significant main or interactive effects.

3.4. Psychosocial provocation (TSST)

TSST response curves are depicted in 5A and B. There were no main or interactive effects of AUD status or race for TSST-induced ACTH. Although including adversity into the model explained a greater proportion of the variance (ACTH: $X^2_4 = 42.2$, p < .0001) no significant main or interactive effects of adversity were present.

The omnibus test for TSST-cortisol revealed no main effect of AUD status. However, a trend level AUD status X race interaction (Fig. 5D: Wilk's $\lambda = .92$, $F_{2,72} = 2.13$, p = .10) appeared. The interaction was driven by group differences in net-integrated response ($F_{1,73} = 5.2$, p = .03) but not basal cortisol (p > .25). Planned pairwise comparisons revealed that White men with AUD exhibited blunted cortisol reactivity relative to White controls (Fig. 5D: $t_{59} = 2.19$, p = .03, d = .45, CI: 19.28–402.51). Within AUD participants, Black men had heightened cortisol reactivity relative to White men ($t_{53} = 1.4$, p = .05, d = .36; CI: -2.37–425.64). Although comparisons with the Black control group did not reach significance (Black control vs. White control: p = .15, d = .66; Black control vs. Black AUD: p = .16, d = .86) the effect sizes were relatively large, suggesting that these analyses may have not been powered to detect group differences in Black controls. Including adversity into the model significantly improved model fit (cortisol: $X^2_4 = 36$, p < .0001), however, no significant main or interactive effects of adversity were present.

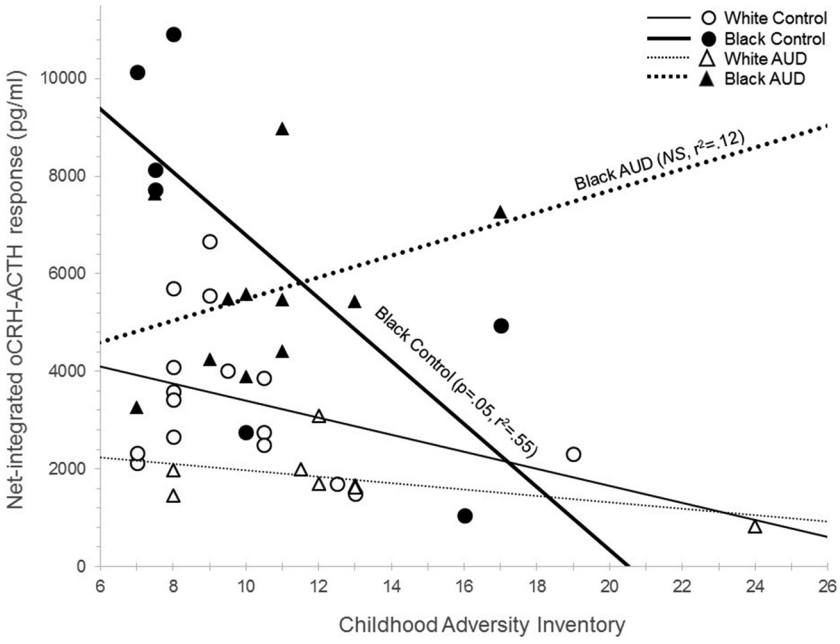

Fig. 3. Three-way interaction between race, group, and childhood adversity (CAI) on oCRH-induced ACTH. Adversity did not influence White participants' net-integrated ACTH response to the oCRH-infusion. A significant interaction between CAI and AUD status was present within Black participants. There was a negative relationship between oCRH-induced ACTH and level of adversity among Black controls ($p = .05$, $r^2 = .55$).

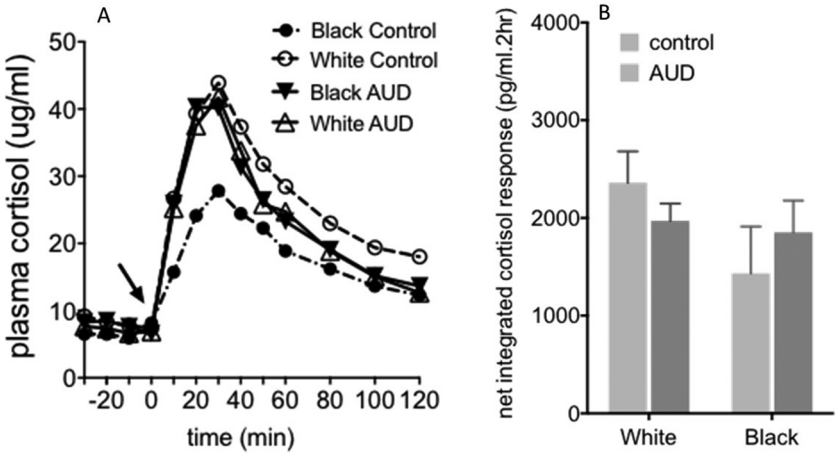

Fig. 4. Cortisol response to cosyntropin. Left panel: Response curves for all groups (A). Arrow indicates the time of infusion. Right panel: Adversity adjusted means for net-integrated cortisol response following cosyntropin are depicted (B). No significant group differences were present.

4. Discussion

The current work served as a secondary examination of the interactive effects between race and AUD status on HPA axis reactivity previously reported (Adinoff et al., 2017). Heightened pituitary sensitivity to administration of oCRH was observed in Black men relative to White men, whereas adrenal sensitivity did not differ between Black and White men. In Black controls only, pituitary sensitivity varied as a function of adversity experienced in childhood. Classically observed main effects of AUD status were not observed in any of our primary analyses. Significant blunting of HPA axis reactivity among individuals with AUD only became apparent when analyzed within White, but not Black, participants and when accounting for childhood adversity. In contrast, Black men with AUD had greater adrenal response to psychosocial stress relative to White men with AUD. This work establishes race-related differences in HPA axis alterations previously identified in AUD.

4.1. Racial differences among healthy controls

These data were uniquely suited to describe the action of the HPA axis when activated at specified functional levels through the use of both a psychosocial stressor and pharmacologic stimulation. It is imperative to acknowledge the differences between TSST-, oCRH-, and cosyntropin-induced activity as the three provocations, by design, activate the HPA axis in differing manners (Herman et al., 2003). The present study revealed that, relative to White control participants, Black controls exhibited dramatic *increases* in pituitary sensitivity to the administration of exogenous CRH but no difference in adrenal sensivity following administration of exogenous ACTH. Additionally, Black controls exhibited modest *decreases* in glucocorticoid activation in response to a psychosocial stressor. These findings provide two pieces of key information: a) Black men (both AUD and controls) have greater pituitary, but not adrenal, sensitivity relative to White men when stimulated by exogenous hormones and b) this heightened pituitary sensitivity is absent in healthy Black men in response to a psychosocial stressor, which activates corticolimbic brain regions prior to hypothalamic stimulation.

Corticolimbic regions [e.g., hippocampus, anterior cingulate cortex (ACC), ventromedial prefrontal cortex] involved in emotional regulation inhibit the HPA axis response to psychosocial stress [e.g. TSST (Radley and Sawchenko, 2015)]. Heightened corticolimbic activation is

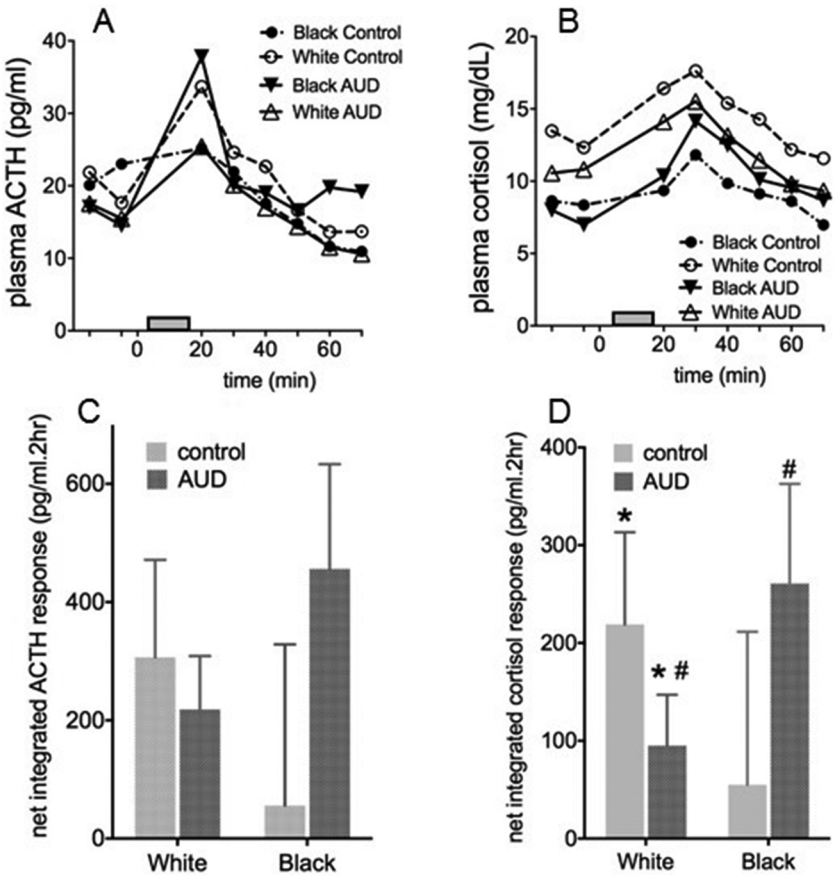

Fig. 5. ACTH and cortisol response to TSST. Top panel: Response curves for ACTH (A) and cortisol (B). Gray box indicates the time that the task occurred. There were no main or interactive effects of group or race on basal or reactive ACTH or on basal cortisol. White men with AUD exhibited blunted TSST-induced cortisol relative to White controls ($p = .03$, $d = .45$). Black men with AUD displayed higher TSST-induced cortisol relative to White men with AUD ($p = .05$, $d = .36$). Bottom Panel: Adversity adjusted means for net-integrated ACTH (C) and cortisol (D) response following the TSST. There were no significant group differences in TSST-induced ACTH. *White men with AUD exhibited blunted TSST-induced cortisol relative to White controls, $p = .03$. #Black men with AUD had higher TSST-induced cortisol than White men with AUD, $p = .05$. Error bars indicate standard error. Note: Y axis for 5C and 5D are ~10% of the oCRH paradigm (Fig. 2C,D).

associated with experiencing aspects of minority stress including social exclusion (Wesselmann et al., 2013), perceived stress (Masten et al., 2011), and discrimination (Akdeniz et al., 2014). Ethnic minority individuals exhibit a high positive correlation between perceived group discrimination and perigenual ACC activation (Akdeniz et al., 2014). Thus, the absence of ACTH hyperactivation in Black controls following the TSST in the current work may be due to greater regulatory inhibition from corticolimbic inputs, thereby mitigating the heightened pituitary response following oCRH stimulation. While central suppression of the HPA axis would be consistent with a protective model of allostatic load (Blaine et al., 2015), we are unaware of any published research associating neural and pituitary reactivity to either behavioral or pharmacological stressors among racially diverse individuals.

The degree to which the differential response in White and Black men can be tied to genetic, epigenetic, or societal and environmental differences requires further systematic evaluation. Though race-specific variants in genotype expression associated with HPA axis function exist (e.g. CRHR1), there is no published research linking altered HPA axis activity in minority individuals to genetic differences. The interaction with adversity from the current study converges with prior work (Geronimus et al., 2006) emphasizing the influence of environmental and societal stress. This body of literature speaks to the long-lasting impact of chronic stress on allostatic systems (Bosch et al., 2012), specifically in racial minorities (Ong et al., 2017; Mulia et al., 2008; Jackson et al., 2016).

While heightened pituitary sensitivity to oCRH administration in Black men and women have previously been observed (Yanovski et al., 1995, 1996), Yanovski and colleagues attributed the heightened ACTH response to detection of biologically inactive fragments of ACTH in Black, but not White, individuals. However, there are differences in design and analysis between the Yanovski work and our study. First, Yanovski et al. (1996) was limited to female subjects while our study included only males. Second, it is unlikely that biologically inactive fragments were detected with our ELISA assay (Biomerica), which was comprised of two antibodies, one that bound $ACTH^{1-24}$ and the other that bound $ACTH^{34-39}$. Only ACTH molecules that bound both antibodies at the same time would be detected and not ACTH fragments.

4.2. Racial differences in AUD-related dysregulation

The current findings describe race-related differential HPA axis activation among treatment-seeking men with AUD, with blunted reactivity limited to White participants. While blunted reactivity is typically noted in both minorities (Chong et al., 2008) and individuals with AUD (Stephens and Wand, 2012; Blaine and Sinha, 2017), simultaneity of the two may lead to increased activity of HPA axis function following psychosocial stress, as seen in the current work. This may be a consequence of the HPA axis reactivity in Whites being primarily driven by their previous alcohol use (resulting in blunted reactivity) whereas HPA axis reactivity in Blacks is driven by a combination of alcohol use and persistent, non-alcohol related stressors. An alternate hypothesis is that the time course of developing blunted HPA axis responsivity is shifted in Black men with AUD, requiring longer periods of abstinence before blunted reactivity is observed. This latter hypothesis is supported by a small but significant breadth of work suggesting that race may play a role in alcohol withdrawal (Brown et al., 1988; Caetano et al., 1998; Blondell et al., 2006; Chan et al., 2009). Further investigation across initiation of abstinence through protracted withdrawal are needed to better clarify the development of these differences.

4.3. Implications

Although the HPA axis activation seen in Black men with AUD is contradictory to our hypotheses of multiplicative hypoactivation, the

current findings align with discrepancies in racially diverse samples observed in the literature. Researchers whose work was foundational in initially establishing the pattern of HPA axis dysregulation in AUD have subsequently failed to replicate the characteristic blunting effects, either noting heightened cortisol response in individuals with AUD or no significant difference between AUD and control groups (Munro et al., 2005; Meng et al., 2011; Sinha et al., 2011). Our review of this work found that the samples producing inconsistent findings were comprised of substantial proportions of racial minority individuals with AUD. Given the interactive effect between race and AUD status identified here, we posit that the use of racially diverse samples has unintentionally restricted the identification of the classically observed AUD-related blunting of the HPA axis.

The divergent pattern seen in Black men with AUD carries significant implications in the trajectories and treatment of AUD. Black individuals with AUD initiate treatment later (Lewis et al., 2017), require longer stays in treatment (Delphin-Rittmon et al., 2012), and are more likely to relapse following abstinence (Zapolski et al., 2014) than White AUD counterparts. Large scale epidemiological studies provide insight into the environmental factors associated with these health disparities (Xanthos et al., 2010); the current work provides a potential biological mechanism underlying racial differences in treatment trajectories.

Lastly, the HPA axis has been identified as a potential target for pharmaceutical therapeutics aiming to increase HPA axis function as a means of decreasing stress-driven craving (Kiefer et al., 2006). For instance, it has been posited that naltrexone may be effective in the treatment of AUD, in part, by removing the tonic opioid inhibition of the hypothalamic CRH release and, in turn, normalizing HPA axis reactivity. If Black individuals with AUD do not demonstrate this blunted response, they may not benefit from this same effect and may, in fact, experience an exacerbated HPA axis response following medication administration. Further investigation of how these treatments may affect minority individuals is imperative in confirming their safety and efficacy.

4.4. Limitations

Because these analyses were exploratory and not initially powered to detect racial differences, individual groups are relatively small and the ability to identify small and medium and small effects are limited. Similarly, the small number of other minority participants in the study restricted analyses to participants who indicated either White or Black with no Hispanic origin. However, the evidence of any significant interactions in this data despite the sample size is provocative. Further, while the overall number of Black participants in this study is relatively small, the number of Black men with AUD (n = 13) is comparable to many of the *full* samples in the most cited AUD and HPA axis literature, independent of race (e.g. Heuser et al., 1988, n = 8; Adinoff et al., 1990, n = 11; Costa et al., 1996, n = 12; Lovallo et al., 2000, n = 10; Adinoff et al., 2005b, c, n = 11;Junghanns et al., 2003, n = 12) and offers sufficient power for a provocation study in a carefully controlled study.

Group differences between controls and AUD participants may be, at least in part, influenced by nicotine use. Recruiting nicotine-using controls from the community is rather challenging, as nicotine use is highly comorbid with other SUDs and psychiatric disorders. It is unclear to what degree our group differences can be explained by differences in nicotine use.

Due to noted gender differences in physiologic and subjective stress reactivity (Adinoff et al., 2010; Kudielka and Kirschbaum, 2005), the larger study was not funded or powered to study female participants. In light of the current findings, possible gender by race interactions are of particular interest. Further studies comparing these differences in women is imperative to understanding how racial disparities affect the stress response system in women with and without AUD.

The degree to which community members are responsive to recruitment methods varies by racial group (e.g. Ashing-Giwa et al., 2004) and requires better understanding. In the absence of stratified recruitment by race, the sample collected was demographically representative of its recruitment area, Dallas-Fort Worth (i.e. 66% White, 21% Black recruited vs. 50% White, 15% Black in the 2010 DFW census), leading the authors to believe that a race-specific selection bias was unlikely. However, this is an important aspect of diversity research and requires further consideration.

More inclusive methods of distinguishing between racial background and minority stress may aid in clarifying nuances of minority status vs. minority stress. Ancestral informative markers (AIMs) may serve as better predictors of ethnicity and prove to be a useful tool in disentangling societal from ethnic differences in future studies. To distinguish between ancestral racial identity and experiences of discrimination, one of many well validated tools assessing minority stress should also be used [e.g. Perceived Racism Scale (McNeilly et al., 1996), the Index of Race-Related Stress (Utsey and Ponterotto, 1996), Experiences of Discrimination (Krieger, 1990)]. Further, minority stress can affect members of any minority group and has been discussed in regards to sexual orientiation (Meyer, 2003) and gender identity (Hendricks and Testa, 2012), particularly in diverse racial groups (Szymanski and Sung, 2010; Balsam et al., 2011). Greater inclusion of other minority groups including sexual, gender, and religious minorities remains to be explored.

4.5. Conclusion

This is the first investigation of racial differences in HPA axis activity among individuals with AUD. Independent of AUD, Black men have 3-fold greater ACTH responsivity following oCRH administration. White men with AUD show decreased cortisol and ACTH activation that is consistent with the literature. However, Black men with AUD displayed no significant decrease in reactivity, and in some cases greater activation than White AUD counterparts. These exploratory findings generate broad concerns over analyses conducted on diverse samples that span other areas of psychiatric research. Previous analyses may have overlooked important subpopulations, and thus, overgeneralized findings to minority groups. Additionally, the consideration of experiential lfie stress is imperative in clarifying the AUD-related alterations in HPA axis function. Future studies will need to be powered to investigate these potential populations of interest.

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References

Adinoff, B., Martin, P.R., Bone, G.H., Eckardt, M.J., Roehrich, L., George, D.T., et al., 1990. Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. Arch. Gen. Psychiatry 47 (4), 325–330.

Adinoff, B., Ruether, K., Krebaum, S., Iranmanesh, A., Williams, M.J., 2003. Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. Alcohol. Clin. Exp. Res. 27 (9), 1420–1427. https://doi.org/10.1097/01.ALC.0000087581.13912.64.

Adinoff, B., Junghanns, K., Kiefer, F., Krishnan-Sarin, S., 2005a. Suppression of the HPA axis stress-response: implications for relapse. Alcohol. Clin. Exp. Res. 29 (7), 1351–1355.
Adinoff, B., Krebaum, S.R., Chandler, P.A., Ye, W., Brown, M.B., Williams, M.J., 2005b. Dissection of hypothalamic-pituitary-adrenal axis pathology in 1-month-abstinent alcohol-dependent men, part 1: adrenocortical and pituitary glucocorticoid responsiveness. Alcohol. Clin. Exp. Res. 29 (4), 517–527.
Adinoff, B., Krebaum, S.R., Chandler, P.A., Ye, W., Brown, M.B., Williams, M.J., 2005c. Dissection of hypothalamic-pituitary-adrenal axis pathology in 1-month-abstinent alcohol-dependent men, part 2: response to ovine corticotropin-releasing factor and naloxone. Alcohol. Clin. Exp. Res. 29 (4), 528–537.
Adinoff, B., Best, S.E., Ye, W., Williams, M.J., Iranmenesh, A., 2010. Adrenocortical and pituitary glucocorticoid feedback in abstinent alcohol-dependent women. Alcohol. Clin. Exp. Res. 34 (5), 915–924. https://doi.org/10.1111/j.1530-0277.2010.01164.
Adinoff, B., Leonard, D., Price, J., Javors, M.A., Walker, R., Brown, E.S., et al., 2017. Adrenocortical sensitivity, moderated by ongoing stress, predicts drinking intensity in alcohol-dependent men. Psychoneuroendocrinology 76, 67–76. https://doi.org/10.1016/j.psyneuen.2016.10.011.
Akdeniz, C., Tost, H., Streit, F., Haddad, L., Wust, S., Schafer, A., Schneider, M., et al., 2014. Neuroimaging evidence for a role of neural social stress processing in ethnic minority-associated environmental risk. JAMA Psychiatry 71, 672–680.
Ashing-Giwa, K.T., Padilla, G.V., Tejero, J.S., Kim, J., 2004. Breast cancer survivorship in a multiethnic sample: challenges in recruitment and measurement. Cancer: Interdiscip. Int. J. Am. Cancer Soc. 101 (3), 450–465.
Balsam, K.F., Molina, Y., Beadnell, B., Simoni, J., Walters, K., 2011. Measuring multiple minority stress: the LGBT people of color microaggressions scale. Cultur. Divers. Ethnic Minor. Psychol. 17 (2), 163.
Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1979. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.
Blaine, S.K., Sinha, R., 2017. Alcohol, stress, and glucocorticoids: from risk to dependence and relapse in alcohol use disorders. Neuropharmacology 122, 136–147.
Blaine, S.K., Seo, D., Sinha, R., 2015. Peripheral and prefrontal stress system markers and risk of relapse in alcoholism. Addict. Biol. 22 (2), 468–478.
Blondell, R.D., Amadasu, A., Servoss, T.J., Smith, S.J., 2006. Differences among those who complete and fail to complete inpatient detoxification. J. Addict. Dis. 25 (1), 95–104.
Bosch, N.M., Riese, H., Reijneveld, S.A., Bakker, M.P., Verhulst, F.C., Ormel, J., Oldehinkel, A.J., 2012. Timing matters: long term effects of adversities from prenatal period up to adolescence on adolescents' cortisol stress response. The TRAILS study. Psychoneuroendocrinology 37 (9), 1439–1447.
Brady, K.T., Waldrop, A.E., McRae, A.L., Back, S.E., Saladin, M.E., Upadhyaya, H.P., et al., 2006. The impact of alcohol dependence and posttraumatic stress disorder on cold pressor task response. J. Stud. Alcohol 67 (5), 700–706.
Breese, G.R., Chu, K., Dayas, C.V., Funk, D., Knapp, D.J., Koob, G.F., et al., 2005. Stress enhancement of craving during sobriety: a risk for relapse. Alcohol. Clin. Exp. Res. 29 (2), 185–195.
Brown, M.E., Anton, R.F., Malcolm, R., Ballenger, J.C., 1988. Alcohol detoxification and withdrawal seizures: clinical support for a kindling hypothesis. Biol. Psychiatry 23 (5), 507–514.
Caetano, R., Clark, C., Greenfield, T., 1998. Prevalence, trends, and incidence of alcohol withdrawal symptoms. Alcohol Health Res. World 22, 73–79.
Chan, G.M., Hoffman, R.S., Gold, J.A., Whiteman, P.J., Goldfrank, L.R., Nelson, L.S., 2009. Racial variations in the incidence of severe alcohol withdrawal. J. Med. Toxicol. 5 (1), 8.
Chong, R.Y., Uhart, M., McCaul, M.E., Johnson, E., Wand, G.S., 2008. Whites have a more robust hypothalamic-pituitary-adrenal axis response to a psychological stressor than blacks. Psychoneuroendocrinology 33 (2), 246–254.
Clark, R., Anderson, N.B., Clark, V.R., Williams, D.R., 1999. Racism as a stressor for African Americans. A biopsychosocial model. Am. Psychol. 54 (10), 805–816.
Delphin-Rittmon, M., Andres-Hyman, R., Flanagan, E.H., Ortiz, J., Amer, M.M., Davidson, L., 2012. Racial-ethnic differences in referral source, diagnosis, and length of stay in inpatient substance abuse treatment. Psychiatr Serv 63 (6), 612–615. https://doi.org/10.1176/appi.ps.201100322.
Derogatis, L.R., Melisaratos, N., 1983. The brief symptom inventory: an introductory report. Psychol Med 13 (3), 595–605.
Dienes, K.A., Hammen, C., Henry, R.M., Cohen, A.N., Daley, S.E., 2006. The stress sensitization hypothesis: understanding the course of bipolar disorder. J. Affect Disord. 95, 43–49.
Fink, L.A., Bernstein, D., Handelsman, L., Foote, J., Lovejoy, M., 1995. Initial reliability and validity of the childhood trauma interview: a new multidimensional measure of childhood interpersonal trauma. Am. J. Psychiatry 152 (9), 1329–1335. https://doi.org/10.1176/ajp.152.9.1329.
First, M.H., Spitzer, R.L., Miriam, G., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P). Biometrics Research Department, New York State Psychiatric Institute, NY.
Geronimus, A.T., Hicken, M., Keene, D., Bound, J., 2006. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. Am. J. Public Health 96 (5), 826–833.
Hajat, A., Diez-Roux, A., Franklin, T.G., Seeman, T., Shrager, S., Ranjit, N., et al., 2010. Socioeconomic and race/ethnic differences in daily salivary cortisol profiles: the multi-ethnic study of atherosclerosis. Psychoneuroendocrinology 35 (6), 932–943.
Heinz, A., Rommelspacher, H., Gräf, K.J., Kürten, I., Otto, M., Baumgartner, A., 1995. Hypothalamic-pituitary-gonadal axis, prolactin, and cortisol in alcoholics during withdrawal and after three weeks of abstinence: comparison with healthy control subjects. Psychiatry Res. 56 (1), 81–95.
Hendricks, M.L., Testa, R.J., 2012. A conceptual framework for clinical work with transgender and gender nonconforming clients: an adaptation of the minority stress model. Prof. Psychol.: Res. Pract. 43 (5), 460.
Herman, J.P., Figueiredo, H., Mueller, N.K., Ulrich-Lai, Y., Ostrander, M.M., Choi, D.C., Cullinan, W.E., 2003. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. Front. Neuroendocrinol. 24 (3), 151–180.
Jackson, J.W., Williams, D.R., VanderWeele, T.J., 2016. Disparities at the intersection of marginalized groups. Soc. Psychiatry Psychiatric Epidemiol. 51 (10), 1349–1359.
Junghanns, K., Backhaus, J., Tietz, U., Lange, W., Bernzen, J., Wetterling, T., et al., 2003. Impaired serum cortisol stress response is a predictor of early relapse. Alcohol Alcohol. 38 (2), 189–193.
Keyes, K.M., Hatzenbuehler, M.L., Hasin, D.S., 2011. Stressful life experiences, alcohol consumption, and alcohol use disorders: the epidemiologic evidence for four main types of stressors. Psychopharmacology 218 (1), 1–17.
Kiefer, F., Jahn, H., Otte, C., Naber, D., Wiedemann, K., 2006. Hypothalamic-pituitary-adrenocortical axis activity: a target of pharmacological anticraving treatment? Biol. Psychiatry 60 (1), 74–76.
Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1993. The' Trier social stress test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28 (1-2), 76–81 doi:119004.
Krieger, N., 1990. Racial and gender discrimination: risk factors for high blood pressure? Soc. Sci. Med. 30, 1273–1281.
Krieger, N., 2005. Stormy weather: race, gene expression, and the science of health disparities. Am. J. Public Health 95 (12), 2155–2160. https://doi.org/10.2105/AJPH.2005.067108.
Kudielka, B.M., Kirschbaum, C., 2005. Sex differences in HPA axis responses to stress: a review. Biol. Psychol. 69 (1), 113–132.
Lewis, B., Hoffman, L., Garcia, C.C., Nixon, S.J., 2017. Race and socioeconomic status in substance use progression and treatment entry. J. Ethnicity Subst. Abuse 1–17.
Lovallo, W.R., Dickensheets, S.L., Myers, D.A., Thomas, T.L., Nixon, S.J., 2000. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. Alcohol. Clin. Exp. Res. 24 (5), 651–658.
Lovallo, W.R., Farag, N.H., Sorocco, K.H., Cohoon, A.J., Vincent, A.S., 2012. Lifetime adversity leads to blunted stress axis reactivity: studies from the Oklahoma family health patterns project. Biol. Psychiatry 71 (4), 344–349.
Masten, C.L., Telzer, E.H., Eisenberger, N.I., 2011. An fMRI investigation of attributing negative social treatment to racial discrimination. J. Cognit. Neurosci. 23, 1042–1051.
McEwen, B., 1998. Stress, adaptation, and disease. Allostasis and allostatic load. Ann. N.Y. Acad. Sci. 840, 33–40.
McNeilly, M.D., et al., 1996. The perceived racism scale: a multidimensional assessment of the experience of White racism among African Americans. Ethn Dis. 6, 154–166.
Meng, D., Wu, T., Rao, U., North, C.S., Xiao, H., Javors, M.A., Adinoff, B., 2011. Serum NPY and BNDF response to a behavioral stressor in alcohol-dependent and healthy control participants. Psychopharmacology (Berl.) 218 (1), 59–67. https://doi.org/10.1007/s00213-011-2414-1.
Meyer, I.H., 2003. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol. Bull. 129 (5), 674.
Miller, W.R., Tonigan, J.S., Longabaugh, R., 1995. In: Mattson, M.E., Marshall, L.A. (Eds.), The Drinker Inventory of Consequences (DrInC) An Instrument for Assessing Adverse Consequences of Alcohol Abuse. National Institutes of Health, Rockville, Maryland.
Mulia, N., Ye, Y., Zemore, S.E., Greenfield, T.K., 2008. Social disadvantage, stress, and alcohol use among black, Hispanic, and white Americans: findings from the 2005 U.S. National Alcohol Survey. J. Stud. Alcohol Drugs 69 (6), 824–833.
Munro, C.A., Oswald, L.M., Weerts, E.M., McCaul, M.E., Wand, G.S., 2005. Hormone responses to social stress in abstinent alcohol-dependent subjects and social drinkers with no history of alcohol dependence. Alcohol. Clin. Exp. Res. 29 (7), 1133–1138.
Ong, A.D., Williams, D.R., Nwizu, U., Gruenewald, T.L., 2017. Everyday unfair treatment and multisystem biological dysregulation in African American adults. Cultur. Divers. Ethnic Minor. Psychol. 23 (1), 27.
Radley, J.J., Sawchenko, P.E., 2015. Evidence for involvement of a limbic paraventricular hypothalamic inhibitory network in hypothalamic-pituitary-adrenal axis adaptations to repeated stress. J. Comp. Neurol. 523 (18), 2769–2787.
Rao, U., Hammen, C., Ortiz, L.R., Chen, L.A., Poland, R.E., 2008. Effects of early and recent adverse experiences on adrenal response to psychosocial stress in depressed adolescents. Biol. Psychiatry 64 (6), 521–526. https://doi.org/10.1016/j.biopsych.2008.05.012.
Sinha, R., Fox, H.C., Hong, K.I., Hansen, J., Tuit, K., Kreek, M.J., 2011. Effects of adrenal sensitivity, stress- and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. Arch. Gen. Psychiatry 68 (9), 942–952. https://doi.org/10.1001/archgenpsychiatry.2011.49.
Skinner, M.L., Shirtcliff, E.A., Haggerty, K.P., Coe, C.L., Catalano, R.F., 2011. Allostasis model facilitates understanding race differences in the diurnal cortisol rhythm. Dev. Psychopathol. 23 (4), 1167–1186. https://doi.org/10.1017/S095457941100054X.
Sobell, L.C., Sobell, M.B., 1992. A technique for assessing self-reported ethanol consumption. In: Allen, J., Litten, R.Z. (Eds.), Measuring Alcohol Consumption: Psychological and Biological Methods. Humana Press, Totowa, N.J, pp. 41–72.
Speilberger, C.D., 1971. Trait-state anxiety and motor behavior. J Mot Behavior 3, 265–279.
Stephens, M.A., Wand, G., 2012. Stress and the HPA axis: role of glucocorticoids in alcohol dependence. Alcohol Res 34 (4), 468–483.
Szymanski, D.M., Sung, M.R., 2010. Minority stress and psychological distress among Asian American sexual minority persons 1Ψ7. Couns. Psychol. 38 (6), 848–872.
Utsey, S.O., Ponterotto, J.G., 1996. Development and validation of the Index of Race-Related Stress (IRRS). J. Couns. Psychol. 43, 490–501.

Wesselmann, E.D., Williams, K.D., Hales, A.H., 2013. Vicarious ostracism. Front. Hum. Neurosci. 7, 153.
Williams, D.R., Mohammed, S.A., 2009. Discrimination and racial disparities in health: evidence and needed research. J. Behav. Med. 32, 20–47.
Xanthos, C., Treadwell, H.M., Holden, K.B., 2010. Social determinants of health among African–American men. J. Men's Health 7 (1), 11–19.
Yanovski, J.A., Yanovski, S.Z., Harrington, L., Gold, P.W., Chrousos, G.P., 1995. Differences in the hypothalamic-pituitary-adrenal axis of black and white men. Hormone Res. Paediatr. 44 (5), 208–212.
Yanovski, J.A., Yanovski, S.Z., Friedman, T.C., Loh, Y.P., Jayasvasti, V., Cutler Jr., G.B., Chrousos, G.P., 1996. Etiology of the differences in corticotropin-releasing hormone-induced adrenocorticotropin secretion of black and white women. J. Clin. Endocrinol. Metab. 81 (9), 3307–3311.
Yzerbyt, V.Y., Muller, D., Judd, C.M., 2004. Adjusting researchers' approach to adjustment: on the use of covariates when testing interactions. J. Exp. Soc. Psychol. 40 (3), 424–431.
Zapolski, T.C., Pedersen, S.L., McCarthy, D.M., Smith, G.T., 2014. Less drinking, yet more problems: understanding African American drinking and related problems. Psychol. Bull. 140 (1), 188.